REMARKS

Claims 22 and 24-35 are pending. Claims 30 and 35 have been canceled. Claims 22, 29, 32, 33 and 34 have been amended and new claims 36, 37, and 38 have been added to more particularly point out and distinctly claim the invention. Support for the amended claims is found, *inter alia,* in the instant specification as originally filed. For example, support for the amendments to claim 1 is found at page 45, lines 11-13, at page 18, lines 12-14, at page 25, lines 6-10, and at page 46, lines 6-23. Support for the amendments to claims 32 and 33 is found in the specification at page 45, lines 11-13, and at page 18, lines 12-14. Support for new claim 36 is found in the specification at page 18, lines 6-15. Support for new claim 37 is found in the specification at page 53, lines 26-29, and at page 56, lines 2-9. Support for new claim 38 is found in the specification at page 27, lines 15-28. Applicants believe that the amendments do not introduce new matter. Accordingly, Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application. Upon entry of the present amendments, claims 22 and 24-38 will be pending and under consideration.

Formalities

The Examiner objected to claims 34 and 35 as allegedly directed to an unelected invention in view of Applicants' election of Group III, drawn to a method for treating HBV infection through modulating cytosolic calcium release, corresponding to claims 22-30 as filed in Applicants' July 18, 2002 Preliminary Amendment and Response to Restriction Requirement, and corresponding to pending claims 22 and 24-33. Specifically, the Examiner asserted that the elected group is restricted to methods which use *only one* compound for treating HBV infection.

Applicants respectfully disagree with the Examiner's assertion. In the June 18, 2002 Restriction Requirement, the Examiner required restriction of the invention to one of six allegedly distinct inventions. Although the Examiner required a further election of one kind of compound to be examined on the merits in connection with an election of Group I, no such requirement was stated in connection with any of the other groups. Accordingly, the Examiner's withdrawal of claims 34 and 35 is improper and Applicants respectfully request that the Examiner rescind that withdrawal. However, Applicants note that, to the extent that the previous amendments to the claims were drawn to compounds

that inhibit Pyk2, the amendments were outside the scope of Applicants' election of Group III. Accordingly, those amendments to the claims are canceled herein.

The Rejections Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

The Examiner rejected claims 22 and 24-33 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

Specifically, the Examiner acknowledged that the instant specification is enabling only with respect to the *in vitro* methods described in the specification, and not with respect to an *in vivo* method for treating patients infected with HBV by administering a compound that modulates cytosolic calcium.

In response, Applicants respectfully disagree with the Examiner's insistence that *in vivo* data is required to support the claimed invention for the reasons of record and for the additional reasons set forth here. Specifically, Applicants maintain that the *in vitro* studies provided in the specification, combined with the knowledge and skill in the art, enable the practice of the claimed methods.

First, Applicants reiterate their position that the *in vitro* assays taught in the specification are recognized in the art as being reasonably predictive for HBV replication *in vivo*. To the extent that the Examiner did not raise this objection again in the current Office Action, Applicants understand the Examiner to agree with their position that a reasonable correlation exists between the *in vitro* models of HBV replication and viral replication *in vivo*. Applicants also point out that the Examiner himself relied on the *in vitro* data provided by Lau to support the Examiner's assertion that the "treatment of [an] HBV patient with cyclosporine is always unpredictable" (see page 3, paragraph 5, of the Office Action mailed March 9, 2004).

Applicants understand the sole remaining basis of the Examiner's rejection to be his view that *in vivo* data is required to support the claimed invention because of an allegedly high degree of unpredictability in the art regarding the *in vivo* use of specific calcium modulating compounds (see page 4, paragraph 5, of the Office Action mailed December 7, 2004). To support this position, the Examiner relied on the art cited in the previous Office Action, namely Lau et al., Transplantation, 1989, 53:894-898, hereinafter "Lau"; Sandrini et al., Nephrol. Dial. Transplant., 1990, 5:525-530, hereinafter "Sandrini";

and Nakanishi et al., Int. Med., 1998, 37:519-522, hereinafter "Nakanishi"). The Examiner also relied on a number of references which purported show that "verapmil, a calcium inhibitor, does not inhibit HBV replication" and instead exhibits liver toxicity and induces hepatitis. Applicants address each of these issues as follows.

According to the Examiner, Lau, Sandrini, and Nakanishi support the proposition that "administration of cyclosporin A [to an] HBV infected patient [produces] unpredictable result[s]" (see page 4, paragraph 5, of the Office Action mailed December 7, 2004). In response, Applicants maintain that the Examiner's reliance on these references to support the alleged unpredictability of the use of cyclosporin is misplaced. In their previous response, Applicants set forth in considerable detail the evidence that the Examiner has misapplied these three references. Applicants note that in the present action, the Examiner failed to address, much less rebut, any of Applicants' arguments on this point. In order to advance prosecution of this application, Applicants briefly summarize their earlier remarks here.

Applicants begin by noting that each of these references teaches the use of cyclosporin as an immunosuppressive agent, a use for which it is well-known in the art. In each reference, either no cyclosporin-dependent effect on HBV is observed, *e.g.*, Lau and Nakanishi, or the reference fails to support the inference that cyclosporin was responsible for the HBV-related clinical observation, *e.g.*, Sandrini. Specifically, Lau teaches that cyclosporin "did not enhance HBV antigen expression" and further that this result was consistent with a number of other reports demonstrating *no effect* of cyclosporin on HBV (see Figure 4 and discussion at page 897, col. 2, to 898, col. 1). Sandrini reports that a subset of renal transplant patients treated with cyclosporin *as an immunosuppressant* developed HBV-related hepatitis, as determined by a positive serological test for HBV DNA. Sandrini makes no statement concerning the effects of cyclosporin on HBV replication. Nakanishi teaches that viral replication is inhibited by interferon alpha, and that cyclosporin is administered *as an immunosuppressant* to prevent complications relating to the onset of autoimmune hepatitis (see page 522, col. 2). Accordingly, Lau, Sandrini, and Nakanishi fail to support the Examiner's assertion that "administration of cyclosporin A [to an] HBV infected patient [produces] unpredictable result[s]."

With respect to the Examiner's allegation that the claimed methods lack enablement because some calcium inhibitors, *e.g.*, verapamil, may demonstrate liver toxicity, Applicants point out that this fact does not support the Examiner's position that undue experimentation is required to practice the claimed methods. The fact that a

compound demonstrates some toxicity does not prevent its use in the claimed methods. Instead, it is well within the skill in the art to balance the expected beneficial aspects of any treatment with its detrimental effects, as determined from routine pharmacological and toxicological studies. The experimentation required to determine an effective therapeutic dose or range of dosages is within routine skill. The specification points to such routine testing as a means for determining a therapeutically effective dose, *e.g., see* pages 45-46.

In summary, Applicants maintain that no undue experimentation is required to practice the methods of the claimed invention and the Examiner has failed to provide sufficient basis to support a rejection on that ground. Accordingly, Applicants respectfully request that the Examiner withdraw his rejection to claims 22 and 24-33 under 35 U.S.C. § 112, first paragraph.

The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 22-27 and 30-33 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Friedrich et al. (Z. Gastroenerol. 1988 26:265-270, hereinafter "Friedrich") under the doctrine of inherency. Specifically, the Examiner asserted that Friedrich inherently anticipates the claimed invention because, in the Examiner's view, administering cyclosporin will always have the effect of "inhibition of cytosolic calcium."

In order to anticipate the claimed invention, a single reference must teach each and every element of the claims. Verdegaal Bros. v. Union Oil Co., 814 F.2d 628 (Fed. Cir. 1987). In order to establish inherency, "the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." In re Robertson, 169 F.3d 743 (Fed. Cir. 1999)(quoting Continental Can Co. v. Monsanto Co., 948, F.2d 1264, 1268, (Fed. Cir. 1991)(internal quotations omitted). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Id. (quoting Continental Can at 1749).

In response to the Examiner's rejection, Applicants submit that Friedrich fails to teach each and every element of the claims, either inherently or expressly. Friedrich fails to demonstrate the inhibition of HBV replication or infection by the administration of cyclosporin. The Examiner has not provided any evidence to establish that the administration of cyclosporin would necessarily inhibit HBV replication in HBV-infected hepatocytes when used in accordance with the method of Friedrich.

Friedrich teaches administering cyclosporin to HBV infected patients in amounts effective to achieve 200-400 ng/ml blood concentration. Friedrich does not teach or suggest administering cyclosporin or any other compound in an amount effective to inhibit cytosolic calcium release and inhibit HBV replication in HBV-infected cells. For example, at page 268, col.1, second full paragraph, Friedrich teaches that the only patient with chronic Hepatitis B that showed any improvements following administration of cyclosporin A, did not demonstrate any improvement or modification of the levels of HBV markers such as HBs-Ag, HBe-Ag, anti-HBc-IgM, and HBV-bound DNA polymerase. Thus, Friedrich does not achieve the inhibition of HBV infection or replication by administration of cyclosporin A. Accordingly, Friedrich fails to anticipate the claimed invention either directly or inherently because the method of Friedrich failed to treat HBV infection or inhibit HBV virus replication, as indicated by Friedrich's own results, which demonstrate that there was no observable change or modification in the levels of HBV markers following administration of cyclosporin A.

In summary, the Examiner's rejection of the claimed invention as expressly anticipated should be reconsidered and withdrawn because the prior art cited by the Examiner fails to disclose each and every element of the claims, *i.e.*, the treatment of HBV infection or inhibition of HBV replication. Likewise, the Examiner's rejection of the claimed invention as inherently anticipated should also be reconsidered and withdrawn, as the missing element, *i.e.*, the treatment of HBV infection or inhibition of HBV replication, is not necessarily present, or inherent, in the prior art reference. *See* Continental Can, *supra*.

In response to the Examiner's rejection of claims 24-27, Applicants understand the Examiner's rejection to be based solely on the dependency of these claims from claim 22. Accordingly, Friedrich fails to anticipate claims 24-27 for the reasons stated above and Applicants respectfully request that this rejection be withdrawn.

In response to the Examiner's rejection of independent claims 30-33, Applicants point out that claim 30 is canceled by this Amendment, rendering the rejection of that claim moot. In response to the rejection of claim 31, Applicants maintain that Friedrich fails to anticipate for the reasons stated above in relation to claim 22. In response to the rejection of claims 32 and 33, Applicants respectfully traverse for the reasons stated above and for the following additional reasons. Specifically, the Examiner has failed to cite any reference that teaches the compounds recited in claims 32 and 33 for use in a method for treating HBV infection. Accordingly, the Examiner has failed to establish a prima facie

case of anticipation with respect to either of claims 32 or 33, and Applicants respectfully request that the Examiner withdraw this rejection.

In summary, Applicants submit that Friedrich fails to anticipate any of claims 22-27 or 30-33, and respectfully request that the Examiner withdraw his rejection of these claims under 35 U.S.C. § 102(b).

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted, by: Jacqueline Benn
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